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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER JABSE, CECILIA M				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/593,543

Applicant(s)

ERIKSSON ET AL.

Examiner

CECILIA M. JAISLE

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 and 15-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 15-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date 05-16-2007
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED OFFICE ACTION

Lack of Unity

Applicant's election without traverse of the invention of Group II, Claims 1-12 and 15-17, drawn to compounds of Formula (I) in which G1 is phenyl, process for preparation thereof, pharmaceutical compositions thereof, and methods of treating disease therewith, in the Response filed on March 11, 2008 is acknowledged. Claims 1-12 and 15-17 are under examination only to the extent that they are directed to the subject matter of Group II; otherwise, non-elected subject matter is withdrawn from examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition *in vitro* of human MMP2, MMP8, MMP9,

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MMP12, MMP14 and MMP19 (pages 40, *inter alia*), does not reasonably provide enablement for treating all obstructive airway diseases (claim 17), treating asthma or chronic obstructive pulmonary disease (COPD) (claim 15) and treating all diseases or conditions mediated by MMP12 and/or MMP9 (claim 16). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following reasons apply to this enablement rejection.

The instant claims cover all obstructive airway diseases and all diseases-conditions mediated by MMP12 and/or MMP9, for which no enablement is provided. The scope of obstructive airway diseases includes all chronic lung diseases, e.g., asthma, COPD, chronic obstructive lung disease, chronic bronchitis or emphysema, in which breathing becomes slowed or forced. The scope of all diseases-conditions mediated by MMP12 and/or MMP9 includes the above listing, as well as certain types of cancer (see Paulus, et al., Cancer Research 66 (8): 4349 (2006)).

Many diseases said to be controlled or protected against by the claimed compounds, such as COPD and cancer, are known as difficult to treat. At present no known drug can successfully prevent or reverse the course of many of these diseases. See European Respiratory Society, http://www.newtocopd.com/currentaffairsnews/list751_item17680.aspx, downloaded 1/15/2008, stating, "... there are currently no effective treatments for COPD ..." Current literature substantiates the inability of researchers to locate a single therapy treatment for all types of cancers. Walsh, BBC News, International Version, Medical Notes, Feb.

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1, 2007, quotes Prof. Fiona Watt, "We've known for many years that not all tumour cells are the same." PharmaLicensing (Mar. 2005), reviewing a number of commercially available cancer treatments, reports:

Effective cancer therapies are focused on the development of agents capable of selectively destroying tumour cells while sparing normal tissues. With this aim, major efforts have been directed at harnessing the specificity of the immune response. The discovery of hybridoma technology in the 1970s enabled the development of tumour-selective monoclonal antibodies (MAbs), creating a targeted therapeutic approach resulting in the selective death of cancer cells. ... Despite the success of currently marketed cancer MAb therapies, however, the dream of a 'magic bullet' of antibody therapy has remained elusive.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq.* This disclosure is not sufficient to enable the claimed methods based solely on the disclosed activity.

MPEP § 2164.01(a) states:

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue

experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration to determine whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) claim breadth; (2) nature of the invention; (3) state of the prior art; (4) level of predictability in the art; (5) amount of direction provided by the inventor; (6) presence of working examples; and (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (CAFC 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement.

1. Breadth of the claims:

(a) Scope of the methods. The claims cover pharmaceutical methods using thousands of substituted 1,2,4-triazol-3-one compounds of Formula (I).

(b) Scope of the diseases covered. The diseases construed by the claims have been described above. The specification fails to identify results of treatment with the methods of this invention or provided prior art teachings which support a direct, correlative connection between MMP inhibition and the treatment of a broad spectrum of diseases and how one would recognize such results.

- 2. Nature of the invention and predictability in the art:** The invention is directed toward medicine and is physiological in nature. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and physiological activity is generally considered an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452 (CAFC 2003).

- 3. Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.
- 4. State of the prior art:** The art indicates the need for undue experimentation.

The discussions above of Paulus, European Respiratory Society, Walsh, Watt and PharmaLicensing are repeated here as equally pertinent.

Molet, et al., *Inflamm. Res.* 54 (2005) 31-36, merely suggests MMP-12 inhibition as an area of possible study in COPD and emphysema, “... this study demonstrated patients with COPD produce greater quantities of MMP-12 than controls, which may be a critical step in the pathogenesis of emphysema.”

Tjwa, et al., *Circulation* 113 (16):1929 (2006) disappointingly report:

Because of their key roles in tissue remodeling and cell infiltration, MMP inhibitors have been considered attractive drug targets. However, most preclinical and clinical studies did not yield the expected result, in part because nonselective inhibitors were used, and several of these MMPs have pleiotropic, sometimes even opposite activities. These failures should not necessarily remove all hope that more selective MMP inhibitors (as have been developed recently for MMP-12) might ever become clinically useful.

This specification (p. 40, *inter alia*) reports these MMP inhibitors are nonselective inhibitors of MMP2, MMP8, MMP9, MMP12, MMP14 and MMP19. The ability of an agent that exhibits activities shown in the specification to treat all diseases-conditions construed by the claims remains open to further study and proof.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests that show a correlation between inhibition of a MMP and the treatment of the conditions recited for the claims. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.
6. **Skill of those in the art:** Paulus, European Respiratory Society, Walsh, Watt, PharmaLicensing, Molet and Tjwa call into question the ability of a single class of compounds to effectively treat all types of diseases and/or conditions construed by the claims; they confirm the need for additional research.
7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained

above. The state of the art, as discussed herein, indicates the requirement for undue experimentation.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

Claims 1-12 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Formula I compounds and their pharmaceutically acceptable salts, does not reasonably provide enablement for solvates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace solvates, are not enabled. The specification prophesizes solvates, but the numerous examples presented all failed to produce a solvate. The evidence of the specification is clear: These compounds do not possess the property of forming solvates; there is no evidence that such solvates even exist.

This is a circumstance where the "specification is evidence of its own inadequacy" (*In re Rainer*, 153 USPQ 802, 807). Solvates cannot be simply willed into existence. *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 states:

The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist ... the examples of the '881 patent do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The same circumstance appears true here: no evidence shows that solvates of these compounds actually exist; if they did, they would have formed. Applicants must show making solvates or limit the claims accordingly.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-12 and 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Because L is required to be a divalent moiety, the monovalent groups (C2 to 6 alkynyl, C2 to 6 alkenyl, C1 to 6 alkyl, C1 to 6 heteroalkyl or C3 to 6 heteroalkynyl) cannot represent this variable. The first definition of G1 as "a monocyclic, bicyclic, tricyclic or tetracyclic group comprising one, two, three or four ring structures each of up to 7 ring atoms; each ring structure being independently selected from cycloalkyl; cycloalkenyl; heterocycloalkyl; unsaturated heterocycloalkyl; aryl; or an aromatic heterocyclic ring" fails to particularly point out and distinctly claim the intended subject matter. It is not possible to determine the number of ring structures and/or whether they are attached to each other or substituents of each other. The term "sulfamino" fails to particularly point out and distinctly claim the intended subject matter. US 20040010022 states inconclusively that examples of sulfamino groups include, but are not limited to, $\text{-NHS(=O)}_2\text{CH}_3$ and $\text{-N(CH}_3\text{)S(=O)}_2\text{C}_6\text{H}_5$. The terms "thiol" and "carbamate" refer to compounds, not substituents. The second definition of G1 as "a bicyclic, tricyclic or tetracyclic group, each ring structure is

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independently joined to the next ring structure by a direct bond, by -O-, by C1-6 alkyl, by C1-6 haloalkyl, by C1-6 heteroalkyl, by C2-6 alkenyl, by C2-6 alkynyl, by sulfone, by CO, by NR7CO, by CONR7, by NR7, by S, or by C(OH), or each ring structure is fused to the next ring structure" fails to particularly point out and distinctly claim the intended subject matter, because it distorts to accepted chemical meaning of bicyclic, tricyclic or tetracyclic. A bicyclic ring structure contains two fused rings. Fusion can occur in three ways: at a single atom (spirocyclic), at two mutually bonded atoms, or across a sequence of atoms (bridgehead). Tri- and tetracyclic ring structures are correspondingly understood. Because the moieties listed as joining one G1 ring structure to the next G1 ring structure are required to be divalent, the monovalent groups (C1-6 alkyl, C1-6 haloalkyl, C1-6 heteroalkyl, C2-6 alkenyl, C2-6 alkynyl) cannot represent this variable.

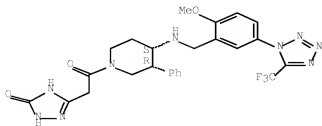
Rejections Under 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, 4, 6, 8, 11, 12 and 16 are rejected under 35 USC 102(a) as anticipated by Ikeura, et al., WO 2003101964 A1, published 2003-12-11, describing RN 632352-46-6, 4-Piperidinamine, 1-[(2,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)acetyl]-N-[[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]phenyl]methyl]-3-phenyl-,



, useful for treatment of frequent urination and urinary incontinence. The definition of G1 in regard to Formula (I) in claim 1 is broad enough to encompass this structure. In regard to claim 16, US 6420119 describes MMPs in treating urinary incontinence.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CECILIA M. JAISLE, J.D. whose telephone number is (571)272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CECILIA M. JAISLE, J.D.

4/10/2008

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624